REMARKS

Claims 32-34, 36, and 39-82 are currently pending in the Application. The Examiner has raised a number of rejections. For clarity, these objections and rejections are listed below in the order in which they will be addressed:

1. Claims 32-34, 36, and 39-82 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite;
2. Claims 32, 33, 39, 47-52, 54, 57, 58, 60, 62, 71-76, and 78 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,118,801 to Lizardi, *et al.*, (hereinafter "Lizardi") in view of Lau, *et al.*, Science 294:858-862 (2001)(hereinafter "Lau");
3. Claims 32, 33, 39, 40, 48-52, 54 and 81 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,770,365 to Lane, *et al.*, (hereinafter "Lane") in view of Lau;
4. 34 and 61 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, in further view of U.S. Patent No. 5,985,557 to Prudent, *et al.*, (hereinafter "Prudent");
5. Claims 36, 39-41, 44-46, 59, and 63-65 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, further in view of Morris, *et al.*, J. Clin. Microbiol., 1996 Dec., 34(12):2933-6, (hereinafter "Morris");
6. Claims 42, 43, 53, 66, 67, and 77 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, further in view of Marras, *et al.*, Genet Anal. 1999 Feb., 14(5-6):151-6 (hereinafter "Marras");
7. Claims 56 and 80 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, in further view of U.S. Patent No. 5,985, 563 to Hyidig-Nielsin, *et al.*, (hereinafter "Hyidig-Nielsin");
8. Claims 81 and 82 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, in further view of U.S. Patent No. 6,027,889 to Barany, *et al.*, (hereinafter "Barany");
9. Claim 81 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lane in view of Lau, and further in view of U.S. Patent No. 5,968,740 to Fodor, *et al.*, (hereinafter "Fodor").

The Claims Are Not Indefinite

1. Claims 32-34, 36, and 39-82 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. In particular, the Examiner asserts that it is unclear what structure is detected in step c), in view of the dissociation of the RNA detection structure recited in step b). Applicants respectfully disagree and respectfully point out that detecting the formation of an RNA detection structure, *i.e.*, that an RNA detection structure has formed *at some point* in the reaction, is not dependent on the continued presence of that RNA detection structure. Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claims 32 and 57 are herein amended to recite that detection of the formation of the detected structure occurs after disassociation. As such, Applicants submit that these claims meet the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request that these rejections be removed.

The Claims Are Not Obvious

Prima facie obviousness requires: 1) a suggestion or motivation in the references or the knowledge generally available to combine or modify the reference teachings; 2) the prior art must teach of a reasonable expectation of success should the suggested combination or modification take place; and 3) the prior art must teach or suggest all the claim limitations. M.P.E.P § 2143. A showing of obviousness will fail if any one of these elements is not met. As explained in more detail below, none of the cited combinations of references cited sets forth each and every element of the rejected claims.

2. Claims 32, 33, 39, 47-52, 54, 57, 58, 60, 62, 71-76, and 78 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau. In particular, the Examiner asserts that the Lizardi teaches a method comprising contacting RNA with an unlabeled probe to form an RNA detection structure.

Applicants respectfully disagree and respectfully point out that the probes of Lizardi are expressly recited to contain a structure (a "switch") that is open upon

hybridization and closed when a target is not hybridized (see, *e.g.*, column 6 at lines 38-43, and Figure 1).

Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claims 32 and 57 are herein amended to recite that the microRNA comprises a 3' terminal end and a 5' terminal end, and that the first region of the unlabeled probe is complementary to a portion of the micro RNA that comprises at least one of these terminal ends. The claims as amended further recite a first portion of the second region of the unlabeled probe is complementary to a second portion of said second region, wherein said first portion and said second portion hybridize to each other to form a duplex when said unlabeled probe is hybridized to said microRNA, and that the duplex and said first region of the unlabeled probe are within one nucleotide of each other. Embodiments of an RNA detection structure as presently claimed are diagrammed, *e.g.*, in Figures 2, 24, and 25. In Figure 24, *e.g.*, probes identified by SEQ ID NOs: 115, 116, and 117 contain first regions complementary to a terminal end of an exemplary microRNA (SEQ ID NO:4) and that are within one nucleotide of the depicted duplex (*e.g.*, adjacent to, or with one nucleotide of overlap, or with a 1 nucleotide gap). The claims are further amended to recite reacting the RNA detection structure with a structure-specific nuclease or a DNA polymerase to form a modified RNA detection structure, wherein said reacting comprises cleaving and/or extending at least one of said probe or said microRNA in said detection structure.

Lizardi does not teach or suggest detection of a nucleic acid, much less a microRNA, using an unlabeled probe having the recited features. Further, Lizardi does not teach or suggest forming an RNA detection structure having the recited features, then modifying the probe and/or the microRNA with a nucleic acid polymerase and/or a structure specific nuclease. Still further, Lizardi does not teach or suggest detection of the formation of an RNA detection structure after disassociation of the microRNA and unlabeled probe.

Lau discloses microRNAs but does not cure the deficiencies of Lizardi with respect to the claimed embodiment of the present invention. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have

been met, Applicants submit that the combination of Lizardi and Lau does not teach or suggest all the limitations of Claims 32, 33, 39, 47-52, 54, 57, 58, 60, 62, 71-76, and 78, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

3. Claims 32, 33, 39, 40, 48-52, 54 and 81 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,770,365 to Lane, *et al.*, (hereinafter "Lane") in view of Lau. In particular, the Examiner asserts that the Lane teaches a method comprising contacting RNA with an unlabeled probe to form an RNA detection structure.

Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claims 32 and 57 are amended herein to recite that the formation of the RNA detection structure detected after the disassociation of the microRNA and the unlabeled probe.

Lane is directed to the detection of presence of a complex between support-bound capture probe and a target nucleic acid. See, *e.g.*, Figures 5, 6, and 7, which pertain to measuring the amount of material bound to the capture probes. Lane does not teach or suggest that detection of the formation of the complex after the disassociation of the complex. Lau discloses microRNAs but does not cure the deficiencies of Lane with respect to the claimed embodiments of the present invention. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Lane and Lau does not teach or suggest all the limitations of Claims 32, 33, 39, 40, 48-52, 54 and 81, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

4-8. Claims 34, 36, 39-46, 53, 56, 59, 61, 63-67, 77, and 80-82 stand rejected under 35 U.S.C. §103(a) under the combinations of references recited below.

Claims 34 and 61 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, in further view of Prudent.

Claims 36, 39-41, 44-46, 59, and 63-65 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, further in view of Morris.

Claims 42, 43, 53, 66, 67, and 77 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, further in view of Marras.

Claims 56 and 80 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, in further view of Hyidig-Nielsin.

Claims 81 and 82 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lizardi in view of Lau, in further view of Barany.

For the reasons recited above, Applicants submit that the combination of Lizardi and Lau fails teach or suggest detection of a microRNA using an unlabeled probe having the features recited in Claims 32 and 57, from which each of the above recited claims depend. Further, the combination of Lizardi and Lau fails teach or suggest forming an RNA detection structure having the recited features, then modifying the probe and/or the microRNA with a nucleic acid polymerase and/or a structure specific nuclease, or detection of the formation of an RNA detection structure after disassociation of the microRNA and unlabeled probe.

Combination of these references with any of Prudent, Morris, Marris, Hydig-Nielsin, or Barany fails to cure these deficiencies. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Lizardi and Lau in view of any of Prudent, Morris, Marris, Hydig-Nielsin, or Barany does not teach or suggest all the limitations of Claims 34, 36, 39-46, 53, 56, 59, 61, 63-67, 77, and 80-82, as called out above, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that each of these rejections be removed.

9. Claim 81 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lane in view of Lau, and further in view Fodor. In particular, the Examiner asserts that the method of heat denaturation and re-naturation of target-probe complexes of Foder satisfies the limitation of a second probe according to Claim 81. For the reasons recited above, Applicants respectfully submit that the combination of Lane and Lau fails to teach or suggest all of the limitations of Claim 32, the claim from which Claim 81 depends. The teachings of Foder fail to cure this deficiency. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met,

Applicants submit that the combination of Lane and Lau in view of Foder does not teach or suggest all the limitations of Claim 81 and therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all objections and rejections have been addressed and should be removed, and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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